

OXYBUTYNIN THERAPYCROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefits of provisional application U.S. Serial No. 60/079,429, filed March 26, 1998 under 35 U.S.C. §119(e).

FIELD OF THE INVENTION

This invention pertains to a novel dosage form comprising oxybutynin. The invention relates also to a therapeutic composition comprising oxybutynin, to a therapeutic bilayer comprising oxybutynin, and to a method for administering oxybutynin to a patient in need of oxybutynin.

BACKGROUND OF THE INVENTION

Many people are affected by urinary incontinence. Incontinence is particularly common in the elderly; urinary incontinence is present in approximately fifty percent of nursing home patients, and urinary incontinence is a well known urologic problem in women. It will affect nearly all women in some form during their lifetime, and it is of significant social concern to all humans who experience it.

Urinary incontinence arises from the anatomy and the physiology of the urinary tract, which is composed of a bladder and a sphincter. Anatomically, the bladder consists of the bladder musculature, also known as detrusor, and the trigone. The sphincter includes the bladder neck and the proximal urethra. The detrusor muscle is innervated by the pelvic nerve through the parasympathetic nervous system, and the bladder neck and proximal urethra are innervated by the sympathetic nervous system.

1           The major functions of the bladder are the storage and expulsion of  
2 urine. The bladder is responsible for accommodating increasing volumes of  
3 urine at low pressures. Normally, the bladder remains closed during bladder  
4 filling and continence is maintained as long as the bladder neck and urethral  
5 pressure exceeds intravesical pressure. Voluntary voiding occurs when  
6 intravesical pressure exceeds bladder neck and urethral pressure, and  
7 involuntary voiding occurs when the intravesical pressure exceeds the  
8 bladder neck and urethral pressure.

9           Involuntary incontinence, also known as urge incontinence, occurs with  
10 a loss of a large volume of urine accompanied by symptoms of urgency,  
11 frequency and nocturia caused by an unstable bladder or detrusor instability.  
12 The patient may lose urine with a change in position or with auditory  
13 stimulation. The loss of small volumes of urine usually occurs because of  
14 bladder overdistention by a large amount of residual urine referred to as  
15 overflow incontinence.

16           The management of incontinence consists in administering a smooth  
17 muscle relaxant, such as oxybutynin, which acts directly on the smooth  
18 muscle at the site distal to the cholinergic receptor. The usual dose in the  
19 pharmacologic management is repeated doses from two-to-four times a day  
20 for oxybutynin. This is difficult to achieve as it requires rigid compliance and it  
21 is cost ineffective. Also, oxybutynin is adversely affected by light and it needs  
22 protection from air, which properties do not lend the drug to formulation into a  
23 dosage form that can administer oxybutynin at a controlled and known rate  
24 per unit time to produce the intended therapy.

25           In light of the above presentation it will be appreciated by those versed  
26 in the medical and pharmaceutical dispensing arts to which this invention  
27 pertains that a pressing need exists for a dosage form and for a therapeutic  
28 composition that can deliver the valuable drug oxybutynin in a controlled,  
29 extended dose to a patient in clinical need of incontinence management. The

1 pressing need exists for an oral dosage form, for a therapeutic composition  
2 and for a method of therapy that can deliver oxybutynin at a controlled rate in  
3 a substantially constant dose per unit time for its beneficial therapeutic effect.  
4 The need exists further for a dosage form and a therapeutic composition that  
5 can deliver oxybutynin protected from light to insure that a complete dose of  
6 oxybutynin is administered to the patient and still remains substantially  
7 independent of the changing environment of the gastrointestinal tract. The  
8 need exists additionally for a dosage form comprising the therapeutic  
9 composition that can deliver a therapeutic dose of oxybutynin for its intended  
10 effect, for avoiding an overdose, and for lessening the side effects that can  
11 accompany the drug. It will be appreciated further by those skilled in the  
12 dispensing art that if such a novel and unique dosage form, therapeutic  
13 composition and method are made available that can administer oxybutynin in  
14 a beneficial dose over time and simultaneously provide oxybutynin while  
15 lessening the incidence of both over and under dose, the dosage form, the  
16 therapeutic composition, and their accompanying methods would represent  
17 an advancement and a valuable contribution to the medical arts.

#### OBJECTS OF THE INVENTION

21 Accordingly, in view of the above presentation it is an immediate object  
22 of this invention to provide a dosage form for delivering oxybutynin in a rate-  
23 controlled dose, and which dosage form substantially overcomes the  
24 deficiencies and omissions associated with the prior art.

25 Another object of the present invention is to provide a dosage form for  
26 orally administering oxybutynin in a controlled dose for the nonsurgical  
27 treatment of incontinence in a human afflicted with incontinence.

1 Another object of the invention is to provide a pharmacologic  
2 composition comprising oxybutynin indicated for the pharmacologic  
3 management of incontinence.

4 Another object of the present invention is to provide a pharmacologic  
5 composition comprising oxybutynin, its racemate, its R-enantiomer and its S-  
6 enantiomer, administrable to a human, for lessening the incidence of  
7 incontinence.

8 Another object of the invention is to provide a dosage form comprising  
9 a homogenous drug core for dispensing oxybutynin to a human patient.

10 Another object of this invention is to provide a novel composition that  
11 makes available oxybutynin therapeutic activity to a patient in need of  
12 oxybutynin therapy.

13 Another object of the invention is to provide a once-a-day oral  
14 sustained release dosage form that delivers a member selected from the  
15 group consisting of oxybutynin and its pharmaceutically acceptable salt at a  
16 controlled rate over 24 hours.

17 Another object of the invention is to provide a dosage form  
18 manufactured as an osmotic dosage form that can administer oxybutynin to a  
19 biological receptor to produce the desired oxybutynin effects.

20 Another object of the present invention is to provide a dosage form  
21 manufactured as an osmotic dosage form that maintains oxybutynin and  
22 oxybutynin therapeutically acceptable salts in the dosage form, and thereby  
23 provides protection from light until the oxybutynin is released from the dosage  
24 form, thereby reducing and/or eliminating the unwanted influences of the  
25 gastrointestinal environment of use and still provide controlled administration  
26 of oxybutynin over time.

27 Another objective of the invention is to provide a sustained release  
28 dosage form that administers oxybutynin at a sustained release rate  
29 accompanied by a lessening of adverse reaction dry mouth.

1 Another object of the present invention is to provide a dosage form that  
2 administers oxybutynin at a controlled rate over time for its therapeutic benefit  
3 accompanied by a lessening of possible unwanted side effects.

4 Another object of the present invention is to provide a dosage form that  
5 contains initially crystalline oxybutynin salt protected by a light resistant,  
6 semipermeable polymeric wall which oxybutynin can be administered in a  
7 controlled dose over time.

8 Another object of the present invention is to provide a dosage form  
9 adapted for the oral administration of  $\alpha$ -cyclohexyl- $\alpha$ -hydroxy-benzeneacetic  
10 acid 4-(diethylamino)-2-butyryl ester salt in a first composition in contacting,  
11 layered arrangement with a second, force-generating composition that  
12 operates in combination for the administration of the beneficial ester salt.

13 Another objective of the invention is to provide a delivery system for a  
14 member selected from the group consisting of oxybutynin and its  
15 pharmaceutically acceptable salt that achieves an increase in the bioavail-  
16 ability of the drug, reduces the formation of its active metabolites, and  
17 achieves a flat drug and metabolite concentration profile as compared to an  
18 immediate release dosage administered multiple times a day.

19 Another object of the present invention is to provide a complete  
20 pharmaceutical oxybutynin regimen comprising a composition comprising  
21 oxybutynin that can be dispensed from a drug delivery dosage form, the use  
22 of which requires intervention only for initiation and possibly for termination of  
23 the regimen.

24 Another object of the invention is to provide a method for treating  
25 incontinence by orally administering oxybutynin from a delivery device in a  
26 rate-controlled amount per unit time to a warm-blooded animal in need of  
27 incontinence therapy.

28 Another object of the invention is to provide a method for lessening the  
29 side-effects accompanying the administration of a member selected from the

1 group consisting of oxybutynin and its pharmaceutically acceptable salts by  
2 administering the drug from a sustained-release dosage form over twenty-four  
3 hours.

4 Another object of the invention is to provide a method of administering  
5 oxybutynin to a patient to provide a plasma concentration of oxybutynin.

6 Another object of the invention is to provide a method for administering  
7 oxybutynin from a controlled-release dosage form for lessening the incidence  
8 of side effects.

9 Another object of the invention is to decrease dry-mouth in a patient  
10 accompanying the administration of a drug selected from the group consisting  
11 of oxybutynin and its pharmaceutically acceptable salts in a sustained-release  
12 dose over twenty four hours.

13 Another object of the invention is to provide a method of administering  
14 oxybutynin in a sustained-release profile to lessen side effects.

15 Other objects, features and advantages of this invention will be more  
16 apparent to those versed in the delivery arts from the following detailed  
17 specification, taken in conjunction with the accompanying claims.

#### 18 19 DRAWING FIGURES OF THE INVENTION

20  
21 Figures 1 to 6 illustrate the clinical benefits for delivering a member  
22 selected from the group consisting of oxybutynin and its pharmaceutically  
23 acceptable salts, according to the invention.

#### 24 25 DETAILED DISCLOSURE OF SPECIFICATION

26  
27 In one aspect, the present invention provides a therapeutic  
28 composition comprising 240 ng to 650 mg (nanogram to milligrams) of  
29 oxybutynin or an oxybutynin therapeutically acceptable salt. The oxybutynin

1 selected from the group consisting of oxybutynin and its pharmaceutically  
2 acceptable salts can be present in a dosage form in, for example, 5 mg, 10  
3 mg, 15 mg, 20 mg, 25 mg, and 30 mg doses and the like. The  
4 pharmaceutically acceptable salt is selected from the group consisting of  
5 acetate, bitartrate, citrate, edetate, edisylate, estolate, esylate, fumarate,  
6 gluceptate, gluconate, glutamate, hydrobromide, hydrochloride, lactate,  
7 malate, maleate, mandelate, mesylate, methylnitrate, mucate, napsylate,  
8 nitrate, pamoate, pantothenate, phosphate, salicylate, stearate, succinate,  
9 sulfate, tannate and tartrate. The drug oxybutynin can be present as the  
10 racemate, as the R-enantiomer or as the S-enantiomer. The therapeutic  
11 composition further contains 20 mg to 250 mg of a hydrogel, such as 20 mg  
12 to 250 mg of a polyalkylene oxide of 75,000 to 600,000 weight-average  
13 molecular weight. Representative polyalkylenes are a polyethylene oxide of  
14 100,000 weight-average molecular weight or a polyethylene oxide of 200,000  
15 weight-average molecular weight. The therapeutic composition comprises 1  
16 mg to 50 mg of a hydroxypropylalkyl-cellulose of 9,000 to 150,000 average-  
17 number molecular weight selected from the group consisting of  
18 hydroxypropylmethylcellulose, hydroxypropylethyl-cellulose,  
19 hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose; 1 mg to 40 mg  
20 of an osmotic solute selected from the osmotically effective compounds  
21 consisting of sodium chloride, potassium chloride, potassium acid phosphate,  
22 tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride,  
23 urea, inositol, sucrose, glucose and sorbitol; and 0.01 mg to 5 mg of a  
24 lubricant, such as calcium stearate, zinc stearate, magnesium stearate,  
25 magnesium oleate, calcium palmitate, sodium suberate, potassium laureate,  
26 salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid,  
27 oleic acid, palmitic acid, and a mixture of salt of fatty, alicyclic or aromatic acid  
28 and a fatty, alicyclic or aromatic acid.

1           The invention provides for the therapeutic composition comprising the  
2 oxybutynin to be administered as the composition neat, that is, oxybutynin  
3 alone, for increasing the urinary bladder capacity, for diminishing the  
4 frequency of uninhibited contractions of the detrusor muscles and its  
5 accompanying delay of the desire to void. The invention provides for the  
6 therapeutic oxybutynin composition to be surrounded by a wall comprising a  
7 semipermeable composition with an exit for delivering the therapeutic  
8 composition to a human patient in need of oxybutynin therapy. The invention  
9 provides, in an additional embodiment, the therapeutic composition  
10 comprising oxybutynin as a therapeutic layer in layered, contacting  
11 arrangement with a hydrogel layer that supports the therapeutic layer to yield  
12 a bilayered matrix. The hydrogel layer comprises 40 mg to 250 mg of a  
13 hydrogel, such as a member selected from the group consisting of 40 mg to  
14 250 mg of a polyalkylene oxide of 1,000,000 to 8,000,000 weight-average  
15 molecular weight which are selected from the group consisting of  
16 polyethylene oxide and polypropylene oxide; or 40 mg to 250 mg of an alkali  
17 carboxymethylcellulose of 10,000 to 6,000,000 weight-average molecular  
18 weight such as sodium carboxymethylcellulose or potassium carboxy-  
19 methylcellulose; or 0.1 mg to 250 mg of a hydroxyalkylcellulose of 7,500 to  
20 4,500,000 weight-average molecular weight, represented by  
21 hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose,  
22 hydroxybutylcellulose, and hydroxypentylcellulose; 1 mg to 50 mg of an  
23 osmagent selected from the group consisting of sodium chloride, potassium  
24 chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose,  
25 magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and  
26 sorbitol; 0 to 5 mg of a colorant, such as ferric oxide; 0.1 mg to 30 mg of a  
27 hydroxypropylalkylcellulose of 9,000 to 225,000 average-number molecular  
28 weight, selected from the group consisting of hydroxypropylethylcellulose,  
29 hydroxypropylpentylcellulose, hydroxypropylmethylcellulose, and



1 hydroxypropylbutylcellulose; 0.00 to 1.5 mg of an antioxidant selected from  
2 the group consisting of ascorbic acid, butylated hydroxyanisole,  
3 butylatedhydroxyquinone, butylhydroxyanisol, hydroxycomarin, butylated  
4 hydroxytoluene, cephalin, ethyl gallate, propyl gallate, octyl gallate, lauryl  
5 gallate, propylhydroxybenzoate, trihydroxybutylphenone, dimethylphenol,  
6 diterlbutylphenol, vitamin E, lecithin and ethanolamine; and 0.1 mg to 7 mg of  
7 a lubricant selected from the group consisting of calcium stearate,  
8 magnesium stearate, zinc stearate, magnesium oleate, calcium palmitate,  
9 sodium suberate, potassium laureate, salts of fatty acids, salts of alicyclic  
10 acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, a mixture  
11 of a salt of a fatty, alicyclic or aromatic acid, and a fatty, alicyclic or aromatic  
12 acid.

13 The invention provides for the therapeutic oxybutynin composition, the  
14 therapeutic bilayer comprising the drug oxybutynin layer, and the  
15 osmopolymer hydrogel layer to be administered as the composition or the  
16 bilayer per se; that is, as the composition or the bilayer together for increasing  
17 the urinary bladder capacity, for diminishing the frequency of uninhibited  
18 contractions of the detrusor muscles and its accompanying delay of the desire  
19 to void. The invention provides additionally for the therapeutic composition  
20 and for the compositional bilayer to be surrounded by a wall comprising a  
21 semipermeable composition with an exit for delivering the therapeutic  
22 composition to a human patient in need of oxybutynin therapy. The invention  
23 also provides for a subcoat to surround the therapeutic composition or to  
24 surround the bilayer, which subcoat in either embodiment is surrounded by a  
25 outer semipermeable wall.

26 The invention provides a dosage form for the delivery of the  
27 therapeutic composition comprising oxybutynin. The dosage form comprises  
28 a wall, which wall surrounds an internal lumen or compartment. The wall  
29 comprises a semipermeable composition that is permeable to the passage of

1 fluid and impermeable to the passage of oxybutynin. The wall is nontoxic and  
2 it comprises a polymer selected from the group consisting of a cellulose  
3 acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose  
4 diacetate and cellulose triacetate. The wall comprises 75 wt% (weight  
5 percent) to 100 wt% of the cellulosic wall-forming polymer; or, the wall can  
6 comprise additionally 0.01 wt% to 10 wt% of polyethylene glycol, or 1 wt% to  
7 25 wt% of a cellulose, either selected from the group consisting of  
8 hydroxypropylcellulose or hydroxypropylalkylcellulose such as hydroxypropyl-  
9 methylcellulose. The total weight percent of all components comprising the  
10 wall is equal to 100 wt%. The internal compartment comprises the  
11 therapeutic oxybutynin composition in layered position with an expandable  
12 hydrogel composition. The expandable hydrogel composition in the  
13 compartment increases in dimension by imbibing fluid through the  
14 semipermeable wall, causing the hydrogel to imbibe the fluid, expand and  
15 occupy space in the compartment, whereby the drug composition is pushed  
16 from the dosage form. The therapeutic layer and the expandable layer act  
17 together during the operation of the dosage form for the release of oxybutynin  
18 to a patient over time. The dosage form comprises a passageway in the wall  
19 that connects the exterior of the dosage form with the internal compartment.  
20 The dosage form provided by the invention delivers oxybutynin from the  
21 dosage form to the patient at a zero order rate of release over a period of 24  
22 hours.

23 The expression "passageway" as used herein comprises means and  
24 methods suitable for the metered release of the therapeutic drug from the  
25 compartment of the dosage form. The exit means comprises at least one  
26 passageway, including orifice, bore, aperture, pore, porous element, hollow  
27 fiber, capillary tube, porous overlay, or porous element that provides for the  
28 osmotic controlled release of oxybutynin. The passageway includes a  
29 material that erodes or is leached from the wall in a fluid environment of use

1 to produce at least one dimensioned passageway. Representative materials  
2 suitable for forming a passageway, or a multiplicity of passageways comprise  
3 a leachable poly(glycolic) acid or poly(lactic) acid polymer in the wall, a  
4 gelatinous filament, poly(vinyl alcohol), leachable polysaccharides, salts and  
5 oxides. A pore passageway, or more than one pore passageway, can be  
6 formed by leaching a leachable compound, such as sorbitol, from the wall.  
7 The passageway possesses controlled-release dimensions, such as round,  
8 triangular, square and elliptical, for the metered release of oxybutynin from  
9 the dosage form. The dosage form can be constructed with one or more  
10 passageways in spaced apart relationship on a single surface or on more  
11 than one surface of the wall. The expression "fluid environment" denotes an  
12 aqueous or biological fluid as in a human patient, including the  
13 gastrointestinal tract. Passageways and equipment for forming passageways  
14 are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864  
15 and 4,816,263. Passageways formed by leaching are disclosed in U.S.  
16 Patent Nos. 4,200,098 and 4,285,987.

17  
18 DESCRIPTION FOR MANUFACTURING THE COMPOSITION  
19 AND DOSAGE FORM OF THE INVENTION  
20

21 The wall of the dosage form can be formed by using the air suspension  
22 procedure. This procedure consists in suspending and tumbling the  
23 composition or the layers in a current of air and wall-forming composition until  
24 a wall is applied to the oxybutynin forming compartment. The air suspension  
25 procedure is well suited for independently forming the wall. The air  
26 suspension procedure is described in U.S. Patent No. 2,799,241; J. Am.  
27 Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and ibid. Vol. 49, pp. 82-84  
28 (1960). The wall can be formed with a wall-forming composition in a Wurster®

1 air suspension coater using an organic solvent, such as acetone-water  
2 cosolvent 90:10 (wt:wt) with 2.5 wt% to 7 wt% polymer solids. An  
3 Aeromatic® air suspension coater using, for example, a methylene dichloride  
4 methanol cosolvent comprising 87:13 (v:v) can be used for applying the wall.  
5 Other wall-forming techniques, such as pan coating, can be used for  
6 providing the dosage form. In the pan coating system, wall forming  
7 compositions are deposited by successive spraying of the composition or the  
8 bilayered arrangement, accompanied by tumbling in a rotating pan. A larger  
9 volume of cosolvent can be used to reduce the concentration of polymer  
10 solids to produce a thinner wall. Finally, the wall of the coated compartments  
11 are laser or mechanically drilled, and then dried in a forced air or humidity  
12 oven for 1 to 3 days or longer to free the solvent. Generally, the walls formed  
13 by these techniques have a thickness of 2 to 20 mils (0.051 to 0.510 mm) with  
14 a preferred thickness of 2 to 6 mils (0.051 to 0.150 mm).

15 The dosage form of the invention is manufactured by standard  
16 manufacturing techniques. For example, in one manufacture the beneficial  
17 drug oxybutynin and other ingredients comprising a therapeutic composition  
18 or comprising the first layer facing the exit means are blended, or they are  
19 blended then pressed, into a solid layer. The oxybutynin and other  
20 ingredients can be blended with a solvent and formed into a solid or semisolid  
21 formed by conventional methods such as ball-milling, calendering, stirring or  
22 roll-milling and then pressed into a selected shape. The layer possess  
23 dimensions that correspond to the internal dimensions of the area the layer is  
24 to occupy in the dosage form. The bilayer possess dimensions  
25 corresponding to the internal lumen of the dosage form. Next, the oxybutynin  
26 hydrogel layer is placed in contact with the oxybutynin drug layer. The  
27 layering of the oxybutynin layer and the hydrogel layer can be fabricated by  
28 conventional press-layering techniques. Finally, the two-layer compartment  
29 forming members are surrounded and coated with an outer wall. A

1 passageway is laser drilled or mechanically drilled through the wall to contact  
2 the oxybutynin layer, with the dosage form optically oriented automatically by  
3 the laser equipment for forming the passageway on the preselected drug  
4 surface.

5 In another manufacture, the dosage form is manufactured by the wet  
6 granulation technique. In the wet granulation technique the oxybutynin and  
7 the ingredients comprising the first layer are blended using an organic or  
8 inorganic solvent, such as isopropyl alcohol-methylene dichloride 80:20 (v:v)  
9 as the granulation fluid. Other granulating fluid, such as water, isopropyl  
10 alcohol, or denatured alcohol 100% can be used for this purpose. The  
11 ingredients forming the first layer are individually passed through a 40 mesh  
12 screen and then thoroughly blended in a mixer. Next, other ingredients  
13 comprising the first layer are dissolved in a portion of the granulation fluid,  
14 such as the cosolvent described above. Then, the latter prepared wet blend  
15 is slowly added to the oxybutynin blend with continual mixing in the blender.  
16 The granulating fluid is added until a wet blend mass is produced, which wet  
17 mass is then forced through a 20 mesh screen onto oven trays. The blend is  
18 dried for 18 to 24 hours at 25°C to 40°C. The dry granules are then screened  
19 with a 16 mesh screen. Next, a lubricant is passed through an 60 mesh  
20 screen and added to the dry screened granule blend. The granulation is put  
21 into milling jars and mixed on a jar mill for 2 to 10 minutes. The first and  
22 second layer compositions are pressed into a layered tablet, for example, in a  
23 Manesty® layer press.

24 Another manufacturing process that can be used for providing the  
25 oxybutynin and hydrogel composition comprises blending their powdered  
26 ingredients in a fluid bed granulator. After the powdered ingredients are dry  
27 blended in the granulator, a granulating fluid, for example,  
28 poly(vinylpyrrolidone) in a solvent, such as in water, is sprayed onto the  
29 respective powders. The coated powders are then dried in a granulator. This

1 process coats the ingredients present therein while spraying the granulating  
2 fluid. After the granules are dried, a lubricant, such as stearic acid or  
3 magnesium stearate, is blended as above into the mixture. The granules are  
4 then pressed in the manner described above. In another embodiment, when  
5 the fluid bed granulating process is used to manufacture the hydrogel layer,  
6 the antioxidant present in the polyalkylene oxide can be removed during the  
7 processing step. If antioxidant is desired it can be added to the hydrogel  
8 formulation; this can be accomplished during the fluid bed granulation  
9 described above.

10 The dosage form of this invention is manufactured in another  
11 embodiment by mixing the oxybutynin with composition-forming ingredients  
12 and pressing the composition into a solid layer possessing dimensions that  
13 correspond to the internal dimensions of the compartment space adjacent to  
14 a passageway. In another embodiment, the oxybutynin and other drug  
15 composition forming ingredients and a solvent are mixed into a solid, or semi-  
16 solid, by conventional methods such as ball-milling, calendering, stirring or  
17 roll-milling, and then pressed into a preselected, layer-forming shape.

18 In the manufactures as presented above, the manufacture comprising  
19 a composition or comprising a layer of a composition comprising a hydrogel  
20 osmopolymer and an optional osmagent are placed in contact with the layer  
21 comprising the drug oxybutynin, and the two layers comprising the layers are  
22 surrounded with a semipermeable wall. The layering of the first drug  
23 oxybutynin composition and the second hydrogel osmopolymer and optional  
24 osmagent composition can be accomplished by using a conventional two-  
25 layer tablet press technique. The wall can be applied by molding, spraying or  
26 dipping the pressed shapes into wall-forming materials. Another technique  
27 that can be used for applying the wall is the air suspension coating procedure.  
28 This procedure consists in suspending and tumbling the two layers in a  
29 current of air until the wall forming composition surrounds the layers.

1 Manufacturing procedures are described in Modern Plastics Encyclopedia,  
2 Vol. 46, pp. 62-70 (1969); and in Pharmaceutical Sciences, by Remington,  
3 14th Ed., pp. 1626-1648 (1970), published by Mack Publishing Co., Easton,  
4 PA. The dosage form can be manufactured by following the teaching in U.S.  
5 Patent Nos. 4,327,725; 4,612,008; 4,783,337; 4,863,456; and 4,902,514.

6 Exemplary solvents suitable for manufacturing the wall, the  
7 composition layers and the dosage form include inert inorganic and organic  
8 solvents that do not adversely harm the materials, the wall, the layer, the  
9 composition and the drug wall. The solvents broadly include members  
10 selected from the group consisting of aqueous solvents, alcohols, ketones,  
11 esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics,  
12 aromatics, heterocyclic solvents and mixtures thereof. Typical solvents  
13 include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol,  
14 butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate,  
15 methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene  
16 glycol monoethyl ether, ethylene glycol monoethylacetate, methylene  
17 dichloride, ethylene dichloride, propylene dichloride, carbon chloroform,  
18 nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether,  
19 cyclohexane, cyclo-octane, toluene, naphtha, 1,4-dioxane, tetrahydrofuran,  
20 diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and  
21 water, acetone and methanol, acetone and ethyl alcohol, methylene  
22 dichloride and methanol, and ethylene dichloride and methanol.

23  
24 DETAILED DISCLOSURE OF EXAMPLES PROVIDED  
25 BY THE INVENTION  
26

27 The following examples are merely illustrative of the present invention  
28 and they should not be considered as limiting the scope of the invention in  
29 any way, as these examples and other equivalents thereof will become

1   apparent to those versed in the art in the light of the present disclosure and  
2   the accompanying claims.

3  
4                                   EXAMPLE 1

5  
6           A therapeutic oxybutynin composition provided by the invention was  
7   prepared as follows: first, 103 grams of oxybutynin hydrochloride was  
8   dissolved in 1200 ml (milliliters) of anhydrous ethanol. Separately, 2,280 g of  
9   polyethylene oxide of 200,000 weight-average molecular weight, 150 g of  
10   hydroxypropylmethylcellulose of 9,200 average-number molecular weight and  
11   450 g of sodium chloride were dry blended in a conventional blender for 10  
12   minutes to yield a homogenous blend. Next, the oxybutynin ethanol solution  
13   was added slowly to the blend, with the blender continuously blending until all  
14   the ingredients were added to the three component dry blend, with the  
15   blending continued for another 8 to 10 minutes. The blended wet  
16   composition was passed through a 16 mesh screen and dried overnight at a  
17   room temperature of 72°F (22.2°). Then, the dry granules were passed  
18   through a 20 mesh screen, 18 g of magnesium stearate was added, and all  
19   the ingredients blended again for 5 minutes. The fresh granules are ready for  
20   formulation into a therapeutic oxybutynin composition. The therapeutic  
21   composition comprises 3.4 wt% oxybutynin hydrochloride, 76 wt%  
22   polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% of  
23   hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 15  
24   wt% sodium chloride, and 0.6 wt% magnesium stearate. The therapeutic  
25   composition can be administered as the composition for its intended  
26   oxybutynin therapy.



EXAMPLE 2

An osmopolymer hydrogel composition provided by the invention was prepared as follows: first 1274 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 weight-average molecular weight, 600 g of sodium chloride, and 20 g ferric oxide were separately screened through a 40 mesh screen. Then, all the screened ingredients were mixed with 100 g of hydroxypropylmethylcellulose of 11,200 average-number molecular weight to produce a homogenous blend. Next, 300 ml of denatured anhydrous alcohol was added slowly to the blend with continuous mixing for 5 minutes. Then, 1.6 g of butylated hydroxytoluene was added, followed by more blending, with 5 g of magnesium stearate added with 5 minutes of blending, to yield a homogenous blend. The freshly prepared granulation is passed through a 20 mesh screen and allowed to dry for 20 hours at 22.2°C. The final composition comprised 63.67 wt% polyethylene oxide of 7,500,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% ferric oxide, 5 mg hydroxypropylmethylcellulose of 11,2000 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 mg magnesium stearate.

EXAMPLE 3

An osmopolymer hydrogel composition provided by the invention was prepared as follows: first 1274 g of pharmaceutically acceptable sodium carboxymethylcellulose comprising a 5,250,000 weight-average molecular weight, 600 g of sodium chloride, and 20 g ferric oxide were separately screened through a 40 mesh screen. Then, all the screened ingredients were mixed with 100 g of hydroxypropylmethylcellulose of 11,200 average-number molecular weight and 100 g of hydroxypropylcellulose of 30,000 average-number molecular weight to produce a homogenous blend. Next, 300 ml of

denatured anhydrous alcohol was added slowly to the blend with continuous mixing for 5 minutes. Then, 1.6 g of butylated hydroxytoluene was added, followed by more blending, with 5 g of magnesium stearate added with 5 minutes of blending, to yield a homogenous blend. The freshly prepared granulation was passed through a 20 mesh screen and allowed to dry for 20 hours at 22.2°C. The final composition comprised 58.67 wt% the sodium carboxymethylcellulose, 30 wt% sodium chloride, 1 wt% ferric oxide, 5 mg of hydroxypropylmethylcellulose, 5 mg hydroxypropylcellulose, 0.08 wt% butylated hydroxytoluene, and 0.25 mg of magnesium stearate.

#### EXAMPLE 4

The therapeutic oxybutynin composition and the osmopolymer hydrogel composition were made into a bilayer tablet as follows: first, 147 mg of the oxybutynin composition as prepared in Example 1 was added to a punch die set and tamped. Then, 98 mg of the hydrogel composition as prepared in Example 2 was added and the two layers compressed under a pressure head of 1.0 ton (1000 kg) into a 11/32 inch (0.873 cm) diameter, contacting intimate bilayered tablet. The example was repeated with the hydrogel composition as prepared in Example 3 to produce the tablet comprising two layers.

#### EXAMPLE 5

The bilayered tablet was manufactured into a sustained-release dosage form that provides a controlled-release of oxybutynin as follows: first, a semipermeable wall-forming composition was prepared comprising 95 wt% cellulose acetate having a 39.8% acetyl content and 5 wt% polyethylene glycol having a number-average molecular weight of 3350 by dissolving the

1 ingredients in a cosolvent comprising acetone and water in 90:10 wt:wt  
2 composition to make a 4% solid solution. The wall-forming composition was  
3 sprayed onto and around the bilayered cores as prepared in Examples 2 and  
4 3 to provide a 26.4 mg semipermeable wall.

5 Next, the semipermeable walled, bilayered tablet was laser drilled to  
6 provide a 20 mil (0.51 mm) orifice to contact the oxybutynin layer and the  
7 exterior of the dosage form. The residual solvent was removed by drying for  
8 48 hours at 50°C and 50% relative humidity. Next, the dosage forms were  
9 dried further for 1 hour at 50°C to remove excess moisture. The dosage form  
10 provided by this manufacture provides 3.4 wt% oxybutynin hydrochloride, 76  
11 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt%  
12 hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.6  
13 wt% magnesium stearate, and 15 wt% sodium chloride in the therapeutic  
14 oxybutynin composition. The osmopolymer hydrogel push composition  
15 comprises 63.67 wt% polyethylene oxide of 7,500,000 weight-average  
16 molecular weight, 30 wt% sodium chloride, 1 wt% ferric chloride, 5 wt%  
17 hydroxypropylmethylcellulose of 9,200 average-number molecular weight,  
18 0.08 wt% butylated hydroxytoluene, and 0.25 wt% magnesium stearate. The  
19 semipermeable wall comprises 95 wt% cellulose acetate comprising 39.8%  
20 acetyl content, and 5 wt% polyethylene glycol of 3350 number-average  
21 molecular weight. The dosage form comprises an exit passage of 20 mils  
22 (0.50 mm) and it has a mean release rate of 0.260 mg/hr for 23.8 hours. The  
23 semipermeable wall provides substantial protection from photo (light)  
24 degradation of the oxybutynin in the dosage form.

#### 25 26 EXAMPLE 6

27  
28 A dosage form is prepared according to the above examples,  
29 comprising a drug layer consisting of 6.67 wt% oxybutynin hydrochloride,

1 87.83 wt% polyethylene oxide of 200,000 weight-average molecular weight,  
2 5.00 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular  
3 weight, and 0.50 wt% magnesium stearate; in layered contact with a push  
4 hydrogel layer comprising 58.75 wt% sodium carboxymethylcellulose of  
5 6,000,000 weight-average molecular weight, 30 wt% sodium chloride, 5.00  
6 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular  
7 weight, 1.00 wt% ferric oxide, 5.00 wt% hydroxypropylcellulose of 75,000  
8 average-number molecular weight and 0.25 wt% magnesium stearate; which  
9 bilayered core is surrounded by a semipermeable wall comprising cellulose  
10 acetate and polyethylene glycol; and an exit port through the wall for  
11 delivering the oxybutynin at a controlled rate over thirty hours.

#### 12 13 EXAMPLE 7

14  
15 The dosage form according to Example 6 wherein the polyethylene  
16 oxide has a 300,000 weight-average molecular weight; the  
17 hydroxypropylcellulose is a member selected from the group consisting of  
18 25,000, 30,000 or 40,000 average-number molecular weight; and the dosage  
19 form comprises 5 mg to 250 mg of oxybutynin pharmaceutically acceptable  
20 salt.

#### 21 22 EXAMPLE 8

23  
24 A dosage form was prepared according to the above examples  
25 wherein the dosage form of this example comprises a drug oxybutynin layer  
26 comprising 5 mg oxybutynin, 111.60 mg polyethylene oxide of 200,000  
27 weight-average molecular weight, 7.35 mg hydroxypropylmethylcellulose of  
28 9,200 average-number molecular weight, 0.88 mg magnesium stearate, 22.05  
29 mg of sodium chloride, and 0.12 mg of butylated hydroxytoluene; a hydrogel

1 push layer comprising 62.40 mg of polyethylene oxide of 7,000,000 weight-  
2 average molecular weight, 29.40 mg of sodium chloride, 4.90 mg  
3 hydroxypropylmethylcellulose of 9,200 average-number molecular weight,  
4 0.08 mg of butylated hydroxytoluene, 0.98 mg of red ferric oxide, and 0.24 mg  
5 of magnesium stearate; a wall comprising cellulose acetate consisting of a  
6 39.8% acetyl content and polyethylene glycol of 3350 number-average  
7 molecular weight in the percentage ratio of 95 wt% cellulose acetate to 5 wt%  
8 polyethylene glycol, and an exit passageway in the wall.

#### 9 10 EXAMPLE 9

11  
12 A dosage form was prepared according to the examples provided by  
13 this invention wherein the dosage form comprises: a drug oxybutynin layer  
14 comprising 5.3 wt% oxybutynin, 82.37 wt% polyethylene oxide of 200,000  
15 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of  
16 9,200 average-number molecular weight, 0.25 wt% magnesium stearate, 10  
17 wt% sodium chloride, and 0.08 wt% butylated hydroxytoluene; a push  
18 hydrogel layer comprising 63.37 wt% polyethylene oxide of 2,000,000 weight-  
19 average molecular weight, 30 wt% sodium chloride, 5 wt% hydroxypropyl-  
20 methylcellulose of 9,200 average-number molecular weight, 0.08 wt%  
21 butylated hydroxytoluene, 1 wt% black ferric oxide and 0.25 wt% magnesium  
22 stearate; a wall comprising 99 wt% cellulose acetate comprising a 39.8%  
23 acetyl content and 1 wt% polyethylene glycol of 3350 number-average  
24 molecular weight; and an exit passageway through the wall for delivering the  
25 oxybutynin to a patient.

EXAMPLE 10

An oxybutynin composition was prepared according to the above examples, wherein the composition comprises 10.6 wt% oxybutynin hydrochloride, 79.57 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.25 wt% of magnesium stearate, 7.5 wt% of sodium chloride, and 0.08 wt% butylated hydroxytoluene.

EXAMPLE 11

An oxybutynin composition was prepared according to the above examples wherein the composition comprises 16 wt% oxybutynin hydrochloride, 76.67 wt% polyethylene oxide of 200,000 weight-average molecular weight, 2 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.25 wt% magnesium stearate, 5 wt% sodium chloride and 0.08 wt% butylated hydroxytoluene.

EXAMPLE 12

A hydrogel composition was prepared according to the above examples wherein the composition comprises 58.75 wt% hydroxyethyl-cellulose of 1,300,000 molecular weight, 30 wt% sodium chloride, 10 wt% polyvinylpyrrolidone of 42,000 viscosity-average molecular weight, 1 wt% red ferric oxide, and 0.25 wt% magnesium stearate.

EXAMPLE 13

A dosage form was prepared according to the present invention wherein the dosage form comprises: a drug layer comprising 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.6 wt% magnesium stearate, 15 wt% sodium chloride; a push hydrogel layer comprising 58.75 wt% hydroxyethylcellulose of 1,300,000 average-number molecular weight, 30 wt% sodium chloride, 10 wt% polyvinylpyrrolidone of 42,000 viscosity-average molecular weight, 1 wt% red ferric oxide, and 0.25 wt% magnesium stearate; a wall comprising 95 wt% cellulose acetate comprising a 39.8% acetyl content, and 5 wt% polyethylene glycol of 3350 number-average molecular weight, an exit orifice of 20 mil (0.50 mm); and a release rate of 0.292 mg per 1 hour for 16.9 hours.

EXAMPLE 14

A dosage form was manufactured according to the present examples wherein the dosage form comprises: a drug oxybutynin layer comprising 3.4 wt% oxybutynin hydrochloride, 76 wt% polyethylene oxide of 200,000 weight-average molecular weight, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.6 wt% of magnesium stearate, and 15 wt% sodium chloride; a push hydrogel layer for pushing the drug oxybutynin layer from the dosage form comprising 63.67 wt% polyethylene oxide of 7,000,000 weight-average molecular weight, 30 wt% sodium chloride, 1 wt% red ferric oxide, 5 wt% hydroxypropylmethylcellulose of 9,200 average-number molecular weight, 0.08 wt% butylated hydroxytoluene, and 0.25 wt% magnesium stearate; a subcoat that surrounds the drug oxybutynin layer and

1 push hydrogel layer wherein the subcoat comprises 95 wt% hydroxyethyl-  
2 cellulose, a nonionic water soluble polymer of 90,000 average-number  
3 molecular weight; a wall or overcoat comprising 95 wt% cellulose acetate  
4 possessing an acetyl content of 39.8% and 5 wt% polyethylene glycol of 3350  
5 number-average molecular weight; a 20 mil (0.50 mm) exit passageway; and  
6 an oxybutynin release rate of 0.295 mg per 1 hour over 19.9 hours.

#### 7 8 EXAMPLE 15

9  
10 A sustained-release dosage form manufactured as a tablet designed  
11 for oral administration comprising 240 ng to 650 mg of a member selected  
12 from the group consisting of oxybutynin and its pharmaceutically acceptable  
13 salts was made according to the above example, which dosage form provide  
14 an essentially flat release profile essentially-free of peaks-and trough plasma  
15 oxybutynin concentrations. The dosage form when administered results in a  
16 lessening in dry mouth over 24 hours, and the bioavailability of oxybutynin in  
17 the lower gastrointestinal tract including the colon.

#### 18 19 METHOD OF PRACTICING THE INVENTION

20  
21 The invention pertains additionally to the use of the therapeutic  
22 composition and the dosage form by providing a method for delivering  
23 oxybutynin orally to a warm-blooded animal, including a human patient, in  
24 need of oxybutynin therapy. The method comprises administering orally the  
25 composition to a patient for oxybutynin therapy. The method comprises: (A)  
26 admitting orally into the patient a dosage form comprising (B) a  
27 semipermeable wall that surrounds (C) a therapeutic composition comprising  
28 (A) oxybutynin. The dosage form imbibes fluid through the wall into the  
29 dosage form in response to the concentration gradient across the



1 semipermeable wall. The therapeutic composition in the dosage form  
2 develops osmotic energy that causes the therapeutic composition to be  
3 administered through the exit (D) from the dosage form over a prolonged  
4 period of time up to 24 hours to provide controlled and sustained oxybutynin  
5 therapy. The method of the invention comprises also: (A) admitting into the  
6 warm-blooded animal a dosage form comprising: (1) a wall surrounding a  
7 compartment, the wall comprising a semipermeable polymeric composition  
8 permeable to the passage of fluid and substantially impermeable to the  
9 passage of oxybutynin; (2) an oxybutynin drug layer in the compartment  
10 comprising oxybutynin; (3) a hydrogel push layer in the compartment  
11 comprising an osmotic formulation for imbibing and absorbing fluid for  
12 expanding in size for pushing the oxybutynin composition from the delivery  
13 device; and (4) at least one passageway in the wall for releasing the  
14 oxybutynin; (B) imbibing fluid through the semipermeable wall at a fluid-  
15 imbibing rate determined by the permeability of the semipermeable wall and  
16 the osmotic pressure across the semipermeable wall causing the push layer  
17 to expand; and (C) delivering the therapeutically active oxybutynin from the  
18 delivery device through the exit passageway to a warm-blooded animal over a  
19 prolonged period of time up to 24 hours. The oxybutynin is administered by  
20 the method of the invention in the therapeutic range that avoids a toxic dose  
21 and avoids an ineffective dose for antispasmodic therapy. The oxybutynin is  
22 administered to patients with uninhibited neurogenic and reflex neurogenic  
23 bladder for increased vesual capacity which diminishes the frequency of  
24 uninhibited contractions of the detrusor muscle and delays the desire to void.  
25 The dosage form is indicated for the relief of symptoms associated with  
26 voiding such as urgency, urge incontinence, frequency, nocturia and  
27 incontinence in patients in neurogenic bladder.

28 The drug oxybutynin, identified as OXY, was administered in a clinical  
29 study to a number of patients. Oxybutynin is used for treating urinary-

1 incontinence. Patients administered oxybutynin often quit or discontinue  
2 treatment in the prior art due to its anti-cholinergic side effects, which appear  
3 to be peak-concentration related. The present invention provides a  
4 sustained-release (SR) dosage form that provides a controlled-release (CR)  
5 rate of oral administration of oxybutynin designed to provide a continuous  
6 plasma drug concentration and avoid peak and valley concentrations. That  
7 is, the controlled-extended release dosage form of this invention maintains a  
8 therapeutic plasma concentration free of an overdose and free of an  
9 ineffective underdose of oxybutynin. In a multiple dose, crossover study, 13  
10 healthy female volunteers of 41 to 68 years of age received either 5 mg of  
11 oxybutynin immediate release (IR) every 8 hours, or three 5 mg controlled  
12 release (CR) once a day, for four days. The patients blood was sampled on  
13 days 1 and 4 to quantify oxybutynin and its desethyl-metabolite (DESOXY) by  
14 liquid chromatography mass spectroscopy (LC/MS). The oxybutynin was  
15 absorbed rapidly following immediate-release (IR) dosing with mean  $C_{MAX}$  of  
16 12 ng/ml.  $C_{MAX}$  is the maximum concentration after dosing in the plasma. The  
17 drug release kinetics for the controlled-release (CR) plasma concentration  
18 rose slowly, reaching a mean peak-concentration  $C_{MAX}$  value of 4.2-6.7 ng/ml.  
19 The metabolite DESOXY was formed rapidly following immediate release,  
20 and its formation paralleled the slow absorption of oxybutynin following  
21 controlled release. The DESOXY had a shorter  $t_{1/2}$  life compared to OXY,  
22 indicating presystemic metabolite formation assuming it to be true metabolite  
23  $t_{1/2}$ . Single and multiple dose AUC values were similar for both the controlled  
24 release and the immediate release suggesting time invariant  
25 pharmacokinetics. AUC denotes the area under the plasma concentration  
26 profile. The day 4 OXY and DESOXY AUC and their ratios are presented in  
27 the Table, where BA denotes the percent bioavailable, that is, BA denotes the  
28 relative amount of oxybutynin absorbed from the controlled release (CR)

dosage form compared to the immediate release (IR) dosage form, and  $C_{MAX}$  denotes the maximum concentration.

	OXY (AUC) (ng.h/mL)	DESOXY (AUC) (ng.h/mL)	OXY/DESOXY Ratio	OXY (BA%)	DESOXY (BA%)
IR	81	483	0.18		
CR	109	304	0.41	153	69

The higher ratio of OXY-BA following CR compared to IR suggests lower metabolic formation on first pass. This indicates CR could reach the colon within 3-5 hours post dosing. Presystemic cytochrome P450-mediated oxidation may occur in the upper part of the gastrointestinal tract; then, drug released from CR in the colon escapes presystemic metabolism, which could explain the higher OXY/DESOXY ratio and increased OXY BA following CR.

A further clinical study was performed that compared the results from a sustained-release dosage form of the invention with an immediate-release dosage form manufactured as a conventional capsule. The study was a double blind placebo controlled comparison in 82 female urge urinary incontinence patients. In the clinical study, 34 of the female patients were administered the sustained release dosage form of the invention, 32 female patients were administered the immediate release dosage form, and 16 were administered placebo. The dosing program for the sustained release dosage form comprised of 5 mg/day for 2 weeks, then 10 mg/day for two weeks, and finally 15 mg/day for two weeks, administered once a day. The dosing program for the immediate release dosage form comprised of 5 mg/day for 2 weeks, then 10 mg/day for two weeks, and finally 15 mg/day for two weeks, administered in divided doses three times a day. During the study decrease in urge urinary incontinence and anticholinergic side effect observations were made for each dose level.

1           The mean plasma oxybutynin concentration was maintained flat during  
2 a 24 hour period for the sustained release dosage form administered once a  
3 day; at steady state (after dosing for 4 days) the mean plasma oxybutynin  
4 concentration ranged from 3.2 to 5.5 ng/ml following a 15 mg dose. The  
5 plasma oxybutynin concentration following the immediate release  
6 administered three times a day showed peak-through fluctuation; at steady  
7 state (after dosing for 4 days) the mean peak plasma concentration following  
8 5 mg three times a day was 12.4 ng/ml and the trough concentration was 1.4  
9 ng/ml. The concentrations at other dose levels are proportional to dose.

10           The clinical study evaluated the number of urge urinary incontinence at  
11 each week. The number of urge urinary incontinence episodes was  
12 documented by the patients in weekly study-diaries provided to them. The  
13 decrease in urge urinary incontinence episodes from baseline was evaluated  
14 for the sustained release dosage form and the immediate release dosage  
15 form compared to the placebo and were also compared to each other.  
16 Efficacy (decrease in urge urinary incontinence) was seen at each dose level  
17 for both sustained release dosage form and immediate release dosage form.  
18 The dose vs. urge urinary incontinence relationship was analyzed by  
19 modeling. The results of the modeling analysis shows a trend towards higher  
20 decrease in the urge urinary incontinence episodes for the sustained release  
21 dosage form compared to immediate release dosage form. Accompanying  
22 Figure 1 depicts the urge-urinary incontinence, U-UI, for patients administered  
23 oxybutynin by the sustained release, SR dosage form tablet of the invention,  
24 by an immediate release, IR, dosage form and a placebo. The figure depicts  
25 the unexpected and striking decrease in urge-urinary incontinence achieved  
26 by the invention. Accompanying Figure 2, depicts the decrease in urge-  
27 urinary incontinence following administration of oxybutynin by the sustained  
28 release dosage form of the invention compared to the immediate release  
29 dosage form.

1           The clinical study considered the anticholinergic side-effect, dry mouth  
2   in the patient; dry mouth was classified using a four scale category consisting  
3   of no-dry mouth, mild dry mouth, moderate dry mouth, and severe dry mouth.  
4   At each weekly clinic visit, patients completed the subjective assessment of  
5   anticholinergic effects questionnaire. In addition, the clinic staff telephoned  
6   patients at other times during the study to solicit information about  
7   anticholinergic effects and other adverse effects. Overall during the study,  
8   the side effect dry mouth was reported in fewer patients receiving the  
9   sustained release formulation (85% of patients) compared to immediate  
10   release formulation (100% of patients). The dose vs. probability of dry mouth  
11   relationship was also analyzed by modeling. This modeling analysis shows  
12   that the probability of dry mouth is higher for the immediate release dosage  
13   form. Accompanying Figure 3 depicts the incidence of dry mouth following  
14   treatment by the sustained release, SR, dosage form, the immediate release,  
15   IR, dosage form, and a placebo. The drawing figure depicts the dose  
16   administered and the degree of dry mouth as none, mild, moderate, and  
17   severe.

18           A therapeutic index was obtained for the clinical study by combining  
19   the dose delivered versus the urge urinary incontinence relationship and the  
20   dose versus dry mouth relationship. Accompanying Figure 4 is a  
21   representation of the therapeutic index comparison between the sustained  
22   release, SR, dosage form and the immediate release dosage form,  
23   evidencing the decrease in urge-urinary incontinence episodes from the  
24   baseline and the probability of dry mouth. In the drawing figure, U-UI denotes  
25   urge-urinary incontinence, DM denotes dry mouth, SR denotes sustained  
26   release and IR denotes immediate release. The broad-double pointed arrow  
27   denotes the unexpected decrease in dry mouth achieved by the sustained  
28   release dosage form compared to the very small decrease in dry mouth seen  
29   in the narrow-double pointed arrow.

1           The therapeutic index is defined as the dose or concentration range  
2 within which optimum therapy with minimum toxicity i.e. successful therapy is  
3 achieved. It can be evaluated as the relative position of the dose vs. efficacy  
4 (urge urinary incontinence in this case) and dose vs. toxicity (dry mouth in this  
5 case) curve. It is also recognized that a drug with wider therapeutic index is  
6 better than a drug with a narrow index.

7           The results of the clinical study are presented in Figures 1 to 4 and  
8 summarized hereafter. Figure 1 shows the urge urinary incontinence in  
9 logarithmic scale for all treatments - the line with the star represents a  
10 placebo treatment, the line connected by square represents urge urinary  
11 incontinence obtained for an immediate release dosage form, and the line  
12 connected with dark circles depicts urge urinary incontinence obtained by the  
13 sustained release dosage form of the invention. In Figure 1, the expression  
14 "U-UI" means urge urinary incontinence, visit day denotes the days the  
15 patient visited the clinic and the dose level denotes the mg of oxybutynin  
16 delivered by the dosage form on that day, "SR" refers to sustained release  
17 dosage form and "IR" refers to immediate release dosage form. As expected  
18 and shown in Figure 1, placebo treatment has really no effect on urge urinary  
19 incontinence episodes. Whereas following both sustained release and  
20 immediate release treatment the number of urge urinary incontinence  
21 episodes decrease. Figure 2 depicts the effect produced by the administered  
22 drug. In this case higher the decrease better the efficacy. In Figure 2, the  
23 solid line which is the decrease in urge urinary incontinence from baseline for  
24 the placebo treatment subtracted from the decrease in urge urinary  
25 incontinence from baseline for the sustained release dosage form and the  
26 dash line which is the decrease in urge urinary incontinence from baseline for  
27 the placebo treatment subtracted from decrease in urge urinary incontinence  
28 from baseline for the immediate release dosage form. Figure 2 shows the  
29 unexpected greater effect in urge urinary incontinence episodes for sustained

1 release dosage form compared to the immediate release dosage form.  
2 Figure 3 depicts the incidence of dry mouth following the administration of  
3 placebo, sustained release oxybutynin dosage forms and immediate release  
4 oxybutynin dosage forms. In the Figure "SR" refers to sustained release  
5 dosage form and "IR" refers to immediate release dosage form, clean area  
6 denotes the probability of absence of dry mouth relief, lines slanted left  
7 denote the probability of mild dry mouth, crossed lines denotes the probability  
8 of severe dry mouth for the administered dose of dry mouth. Figure 4 is a  
9 representation of the therapeutic index comparison between the sustained  
10 release dosage form and the immediate release oxybutynin dosage form.  
11 The therapeutic index is the dose or concentration range within which  
12 optimum therapy with minimum toxicity i.e. successful therapy is achieved. It  
13 can be evaluated as the relative position of the dose vs. efficacy (urge urinary  
14 incontinence in this case) and dose vs. toxicity (dry mouth in this case) curve.  
15 Both the dose vs. urge urinary incontinence curve and the dose vs. dry mouth  
16 curve is presented in Figure 4. The broad continuous dark line presents the  
17 dose vs. urge urinary incontinence relationship for sustained release dosage  
18 form and the narrow continuous line presents the dose vs. urge urinary  
19 incontinence relationship for immediate release dosage form; the broken dark  
20 line represents the occurrence of dry mouth for the sustained release dosage  
21 form and the broken narrow line represents the occurrence of dry mouth for  
22 the immediate release dosage form. The heavy longer dark double pointed  
23 arrow depicts the unexpected greater separation for the dose vs. urge urinary  
24 incontinence curve and the dose vs. dry mouth curve for the sustained  
25 release dosage form compared to the small double pointed arrow for the  
26 immediate release dosage form. This teaches that the therapeutic index is  
27 wider for the sustained release dosage form as compared to immediate  
28 release dosage form.

1       The once-daily delivery system provided by this invention maintains an  
2       essentially flat concentration throughout the dosing duration of 24 hours, as  
3       seen by the absence of peak-to-trough fluctuation, whereas peak-to-trough  
4       fluctuation are seen with the multiple daily administration of the immediate  
5       release dosage form, as depicted in accompanying Figure 5.

6       Figure 5 depicts the mean plasma oxybutynin concentration, in ng/mL,  
7       steady state on day 4, for an immediate release, IR, dosage form and a  
8       sustained release, SR, dosage form.

9       The delivery system provided by this invention maintains its chemical  
10      and physical integrity in a gastrointestinal environment and generally reaches  
11      the colo within 3 to 5 hours after oral administration. For some drugs,  
12      metabolic activity is higher in the duodendum and jejunum and decreases in  
13      the ileum and colon and for some drugs other anti-transport are more  
14      prevalent in the colon. The physiological disposition of a drug and its  
15      metabolites can depend on the gastrointestinal site of absorption. The clinical  
16      studies made available by this invention demonstrated unexpectedly a  
17      decrease in oxybutynin metabolism when administered by the sustained  
18      release dosage form of the invention. Following the administration of  
19      oxybutynin chloride according to the mode and manner of the invention, the  
20      relative bioavailability is higher for the drug, combined R+S (racemic)  
21      oxybutynin (153%) and also for the individual R- and S- enantiomers of  
22      oxybutynin (156% and 187%, respectively) compared to immediate release  
23      dosage form (base of 100%); the relative bioavailability is lower for the  
24      metabolite, combined R+S (racemic) desethyloxybutynin (69%) and also for  
25      the individual R- and S- enantiomers of desethyloxybutynin (73% and 92%,  
26      respectively) compared to immediate release dosage form (base of 100%).  
27      The relative bioavailability is defined as the following ratio, wherein the  
28      Relative Bioavailability for SR =  $[Total\ AUC_{inf}(SR) + Dose(SR)] / [Total$   
29       $AUC_{inf}(IR) + Dose(IR)]$  where  $AUC_{inf}(SR)$  is the area under the plasma



1 concentration curve for the sustained release dosage form and  $AUC_{inf}(IR)$  is  
2 the area under the plasma concentration curve for the immediate release  
3 dosage form. The plasma concentration curves are shown in Figure 5 for  
4 both sustained release dosage form and the immediate release dosage form.  
5 The ratio,  $(\text{drug } AUC_{inf} / \text{metabolite } AUC_{inf})$  for the sustained release dosage  
6 form was more than twice that for the immediate release. It has been  
7 hypothesized that oxybutynin metabolites may be responsible for the side  
8 effects (Massad et al, J Urol 1992;148:595-597), however, both drug and the  
9 metabolite desethoxybutynin have been shown to have similar potency  
10 (Waldeck et al, J Urol 1997;157:1093-1097). The clinical study demonstrated  
11 further for an immediate release oxybutynin system, following repeated  
12 dosing within a day, the peak drug concentrations are lower in the evening as  
13 compared to morning drug administration. This suggests that with a zero-  
14 order release rate from a sustained release dosage form, the plasma  
15 concentration would go down towards the end of the day. However for the  
16 dosage forms provided by this invention delivering oxybutynin hydrochloride it  
17 is not the case. On the contrary, with the dosage forms provided by this  
18 invention, the plasma concentrations in an essentially steady-state are  
19 maintained throughout the day ranging from 3.2 to 5.5 ng/mL following a 15  
20 mg dose. Additionally, the plasma concentration for the sustained release  
21 dosage form of the invention administered in the fasting state is similar to that  
22 observed when taken after a meal as seen in drawing Figure 6. Drawing  
23 Figure 6 illustrates the mean observed plasma R-oxybutynin concentration  
24 following the sustained delivery of oxybutynin hydrochloride by the dosage  
25 form tablet of the invention 1 X 10 mg qd, wherein qd denotes once-a-day  
26 dose, in the fed and fasting states with 43 patients. The data shows food  
27 does not affect the manner in which the drug is absorbed from the sustained  
28 release dosage form of the invention. Whereas, another delivery product for  
29 oxybutynin reported by (Lukkari et al, Eur J Pharmacol, 1996; 50:221-223:

1 Lukkari et al, 1997; 81:31-34; Nilsson et al, Neurol Urodyn,1997;16:533-542)  
2 has properties very different from the sustained release dosage form of this  
3 invention. The prior art product is a matrix tablet from which the drug is  
4 released by a first order process with about 50% released in 4 hours. The  
5 relative oxybutynin bioavailability for the product is similar (approximately  
6 103%) to that of the immediate release product (base 100%) and the relative  
7 bioavailability of the metabolite desethyloxybutynin is lower (approximately  
8 68%) as compared to immediate release product (base 100%). The ratio,  
9 (drug AUC / metabolite AUC) for the product was only slightly higher (0.13) as  
10 compared to IR oxybutynin (0.09). Additionally, when the prior art product is  
11 taken after meals the peak oxybutynin (6.2 ng/mL) and desethyloxybutynin  
12 concentration (75.5 ng/mL) are two times higher as compared to the fasting  
13 state (2.8 ng/mL and 39.5 ng/mL, for oxybutynin and desethyloxybutynin  
14 respectively). That is, the prior art delivery product loses the sustained  
15 release property when taken with meals.

16 The sustained release dosage form of the invention was further  
17 evaluated in safety and efficacy studies and compared to immediate release.  
18 The data from this study was modeled and a dose vs. therapeutic effect (urge  
19 urinary incontinence) relationship and a dose vs. side effect (dry mouth)  
20 relationship was established. The results of the urge urinary incontinence  
21 modeling analysis shows a trend towards higher decrease in the urge urinary  
22 incontinence episodes for the sustained release dosage form compared to  
23 immediate release dosage form. The dry mouth modeling analysis shows  
24 that the probability of dry mouth is higher for the immediate release as  
25 compared to the sustained release dosage form of this invention. A  
26 therapeutic index was obtained for the clinical study by combining the dose  
27 versus the urge urinary incontinence relationship and the dose versus dry  
28 mouth relationship. The therapeutic index is defined as the dose or  
29 concentration range within which optimum therapy with minimum toxicity i.e.

1 successful therapy is achieved. It can be evaluated as the relative position of  
2 the dose vs. efficacy (urge urinary incontinence in this case) and dose vs.  
3 toxicity (dry mouth in this case) curve. The sustained release dosage form of  
4 this invention was shown to have an increased therapeutic index (wider  
5 separation between the dose vs. urge urinary incontinence curve and dose  
6 vs. dry mouth curve) as compared to the immediate release dosage form, as  
7 seen in Figure 4. In two additional clinical trials, a SR was administered in  
8 doses up to and comprising 30 mg/day which was efficacious in reducing  
9 urge urinary incontinence and was well-tolerated with respect to  
10 anticholinergic side-effects and especially dry mouth.

11 In conclusion, the sustained release dosage form of this invention, the  
12 oxybutynin plasma concentrations are maintained constant avoiding the rapid  
13 rise and peak concentration seen with immediate release oxybutynin, the  
14 metabolism of the drug is reduced giving rise to higher oxybutynin  
15 bioavailability compared to immediate release oxybutynin and the sustained  
16 plasma concentrations are not affected by meals taken with the drug. Finally,  
17 the sustained release dosage form of this invention has an increased  
18 therapeutic index as compared to immediate release oxybutynin.

19 The dosage form and the oxybutynin composition of this invention, as  
20 seen from the above disclosure, can be used in a method for administering a  
21 drug by the oral route, and, in another method, the dosage form and  
22 composition can be sized and shaped for administering a drug by the  
23 sublingual and buccal routes. The sublingual and buccal routes can be used  
24 for quicker therapy, and they can be used when a smaller dose of drug is  
25 needed for immediate therapy. The latter routes can be used as a by-pass of  
26 the first pass of hepatic metabolism of the drug.

27 In summary, it will be appreciated that the present invention  
28 contributes to the art an unobvious dosage form that possesses practical  
29 utility, can administer a drug at a dose-metered release rate per unit time.

1 While the invention has been described and pointed out in detail with  
2 reference to operative embodiments thereof, it will be understood by those  
3 skilled in the art that various changes, modifications, substitutions and  
4 omissions can be made without departing from the spirit of the invention. It is  
5 intended, therefore, that the invention embrace those equivalents within the  
6 scope of the application.

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